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Mercury pollution in modern times and its socio-medical consequences

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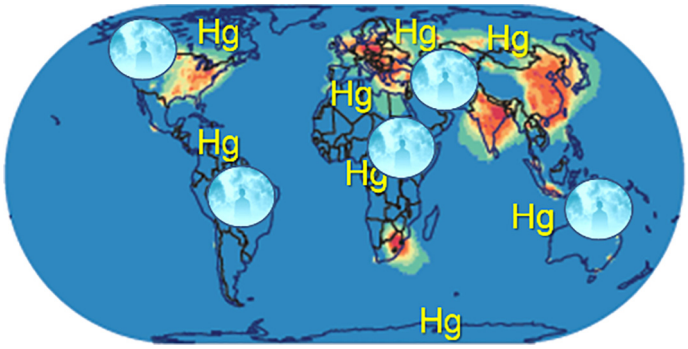
HIGHLIGHTS

- Mercury pollution poses global human health and environmental risks. Still knowledge gaps exists on both exposures and health effects and translation into preventive actions is delayed.
- Across the globe, differences in mercury contamination and related health effects exist. Understanding the risks associated with mercury exposure is complicated by this element's varied environmental fate and the overarching influences of environmental, biological, and socioeconomic drivers.
- Successful management of global and local mercury pollution and its health impact will require integration of mercury research and policy in a changing world. Research should be swiftly translated in adequate preventive measures and human biomonitoring programs.
- The lesions learned from Minamata show that, there is a need for accurate information about contaminant exposures enabling policymakers to make informed choices (i.e. that balance the benefits of fish consumption against the adverse effects of low-level methyl mercury exposures).

GRAPHICAL ABSTRACT



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ABSTRACT

Mercury plays a critical role in serious health problems due to environmental or occupational exposures. Aquatic ecosystems are an essential component of the global biogeochemical cycle of mercury, as inorganic mercury can be converted to toxic methyl mercury in these environments and reemissions of elemental mercury rival anthropogenic mercury releases on a global scale.
The history of the Minamata disease, a typical example of industrial pollution, has shown how corporate secrecy and ignorance on part of the health authorities may influence the devastating spread of environmental contamination and the progress of disease. While the Minamata Convention, in place since 2017, is aiming to lower mercury exposure and to prevent adverse effects, there are still knowledge gaps in the areas of global environmental

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mercury exposure. Areas of uncertainty in the global biogeochemical cycle of mercury include oxidation processes in the atmosphere, land-atmosphere and ocean-atmosphere cycling, and methylation processes in the ocean. Pollution related to climate change (especially in boreal and arctic regions), bioaccumulation and biomagnification of methyl mercury in the food chain, especially in fish and marine mammals, needs to be addressed in more detail. Information is lacking on numerous hidden contaminant exposures i.e. from globally applied traditional medicine, mercury containing skin creams and soaps, dental amalgam, ethyl mercury containing vaccines and latex paint additives, as well as on mercury releases from power plants, e-waste/fluorescent lamps, wildfire emissions, and global artisanal small-scale gold mining activities.

Mercury occurs in various forms with different levels of toxicity. While much is already known and documented on the health effects of mercury, present knowledge and translation into preventive actions is still incomplete. Risks for long term health effects trough prolonged low dose exposure and trough cumulative exposures of various mercury forms should be further addressed. Preventive actions should include adequate human biomonitoring programs. Research data should be translated swiftly into management tools for local policy makers and health professionals, also paying attention at the major differences in mercury contamination across the globe.

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1. Introduction

Mercury (Hg) is ranked third of the most toxic elements to human health by the United States (US) Government Agency for Toxic Substances and Disease Registry (ATSDR) (ATSDR, 2012). Pure Earth estimates (Pureearth, 2015), that there is a health risk associated with mercury exposure in 19 million people worldwide, with an estimated disease burden of 1.5 million DALYs. In 2015, the Toxic Sites Identification Program identified >450 sites around the world where exposure to mercury threatens the health of the population (Pureearth, 2015). Environmental mercury contamination is an urgent global health threat, however, the complexity of the biogeochemical cycle of mercury can hinder accurate determination of environmental and human health risks (Eagles-Smith et al., 2018).

Progress has been made over the past several decades, resulting in improved inventories of mercury sources and releases and a more robust scientific understanding of the factors influencing mercury's fate and transport, the processes driving methyl mercury production and the manifestations and mechanisms of many of the toxic effects of mercury in biota (Eagles-Smith et al., 2018). This progress has supported global efforts to reduce mercury loading to the environment for protection of human and ecological health, such as those put forth at the Minamata Convention on Mercury, which came into force in 2017 (Obrist et al., 2018; Selin et al., 2018). We now have better insights in some special specific characteristics such as biomagnification and the capacity for crossing the placental and blood-brain barrier.

Human activities have the potential to enhance mercury methylation by remobilizing previously released mercury, and increasing methylation efficiency. The bioaccumulation in aquatic and terrestrial food chains results in elevated exposure to humans and wildlife (Chen et al., 2018). Its long range transport (LRT) makes that mercury can appear even in remote regions in which there are not atmospheric releases (i.e. arctic regions). Recent advances include the availability of new global datasets covering areas of the world where environmental mercury data were previously lacking. Integration of these data into global and regional models is continually improving estimates of global mercury cycling (Obrist et al., 2018). It is anticipated that future emissions changes will be strongly dependent on small-scale handicraft gold mining (ASGM), as well as on energy use scenarios and technology requirements implemented under the Minamata Convention (Obrist et al., 2018). However, alterations of mercury cycling, methyl mercury bioavailability and trophic transfer due to climate and land use changes remain critical uncertainties. In the face of these uncertainties, important policy and management actions are needed over the short-term to support the control of mercury releases to land, water and air (Chen et al., 2018).

Diseases induced after mercury pollution provide a considerable part of the pollution-related diseases, which are responsible for millions of premature deaths (Landrigan et al., 2017), Our aim was to provide an overview of the current knowledge on mercury pollution/exposure and its possible impact on global health, for the special edition: "Pollution in living and working environment and their impact on non-communicable disease burden" (as a part of the multicenter, interdisciplinary EU COST action, DiMoPEx). To elaborate recent data on mercury exposure and its health effects, we have screened and critically reviewed PubMed publications on mercury exposure 2015–2018 (with terms "mercury toxicity" and "mercury poisoning", "mercury exposure": Out of 7700 publications identified, 392 publications from 2015 were screened, 521 from 2016; 344 from 2017 and 344 publications from 2018 [till 07st September 2018]). When relevant, older references and publicly available links were called in. We focus here on recent data spotlighting the toxic element mercury and its environmental pollution and health hazards (with human biomonitoring), providing references to more detailed reviews, relevant original publications and public sources. When necessary, references to older publications are also made available.

1.1. Various mercury species mirror various exposure forms and different toxic effects

Mercury is a heavy metal that occurs in various forms, such as elementary mercury, inorganic and organic compounds with different levels of toxicity and exposure pathways (WHO, 2007). Each of these forms has different impacts on health surveillance and requires different countermeasures to avoid exposure. Elementary mercury (Hg^0), also known as metallic mercury, is oxidized to inorganic mercury (Hg^{2+}), when entering the atmosphere. Elemental mercury in its gaseous form is the predominant form of mercury in the atmosphere with atmospheric lifetime of approximately 6–24 months (UNEP, 2015). It occurs in nature and is mined as mercuric sulphide from cinnabar ore. The metallic form is refined from mercuric sulphide by heating it to 538 °C. This vaporizes the mercury in the ore, and the vapors are then captured and cooled to form the liquid metal mercury. In this form it is used for the production of thermometers, electrical parts, dental fillings as well as for the production of sodium hydroxide and chlorine gas. Inorganic mercury compounds include mercury chloride, mercury acetate and sulphur sulphide. Coal-fired power plants emit both elemental and inorganic mercury (Hg^0 vs. Hg^{2+} ratio, depends on the filter system) (Madsen and Randall, 2011; Streets et al., 2018). The general population is exposed to small amounts of elemental mercury due to its use in dental amalgams (Ruggieri et al., 2017). On the other hand, workers at ASGM sites and gold shops can be exposed to high levels of elemental mercury (Streets et al., 2017).

Air pollution from coal-fired power plants and other coals-burning facilities is linked with asthma in the general population. Acute high dose exposure to elemental mercury may cause severe pneumonitis

(Cortes et al., 2018). A large proportion of inhaled gaseous elemental mercury (approximately 80%) is absorbed into the blood via the lungs, and, as an uncharged and therefore lipid-soluble substance, it can easily pass through the blood-brain barrier. With time, the gaseous elemental mercury in the patient's brain is oxidized to inorganic divalent mercury and causes damage to the brain, and the inorganic mercury also accumulates in the kidneys, where it causes renal damage (Sakamoto et al., 2018).

Exposure to toxic amounts of inorganic mercury is rare. The inorganic salts of mercury are corrosive to the skin, eyes and gastrointestinal tract, and may induce kidney toxicity (renal tubular necrosis), if ingested (WHO, 1991). Neurological symptoms include mental retardation, seizures, vision and hearing loss, delayed development, language disorders and memory loss. In adults the symptoms include tremors, insomnia, memory loss, neuromuscular effects, headaches and cognitive and motor dysfunction (WHO, 2007). Mild subclinical signs of central nervous system toxicity can be seen in workers exposed to elemental mercury. Occupational exposure of chloralkali workers to highly concentrated mercury vapor has been linked to an increased risk of renal dysfunction and behavioral changes. These workers were shown to be exposed to inorganic $HgCl_2$ (Elgazali et al., 2018).

Organic mercury is formed when elemental mercury comes into contact with carbon. Organic mercury is considered as the most hazardous and most frequent form of mercury exposure, which is frequently detected as methyl- or ethyl mercury (Crowe et al., 2017). It is most commonly found in the environment as methyl mercury, a powerful neurotoxin, formed by microorganisms in water from elemental mercury (Braune et al., 2015; Pacyna et al., 2010). Because of its structural properties, methyl mercury accumulates in the fatty tissue of many organisms, including those that serve as food for humans (i.e. fish and marine mammals). Most human methyl mercury exposure occurs from methyl mercury, which is bioaccumulated in food chains (fish, seafood, fish consuming animals). The Minamata disease, which can induce lethal or severely debilitating mental and physical effects, was caused by the methyl mercury-contaminated effluent released into the Minamata Bay by Chisso, and by its bioaccumulation within the food chain (see below for more details) (Sakamoto et al., 2018). Several studies have shown a link between organic-mercury exposure and increased risks of neuro developmental disorders, such as tic disorder, ASD, attention-deficit/hyperactivity disorder (ADHD), and delayed language/speech skills (Hviid et al., 2003; Young et al., 2008). During time organic mercury forms deposited in the brain are metabolized to mercuric Hg (Berlin et al., 2015). Such mercurials may also evoke immunological reactions (Bjorklund et al., 2017). Some methyl mercury combines with L-type cysteine to form L-cysteine-methylmercury conjugates, are then distributed to all tissues, including the brain (via the blood brain barrier), as they are treated like L-type neutral amino acid, methionine (Sakamoto et al., 2018). After equilibration contents of methyl mercury in the brain tissue is about 6 times higher than in blood. Due to the epidemic intoxications with methyl mercury (i.e. Minamata) the brain was the organ that was most severely affected, particularly in that the developing brains of fetuses were damaged (Sakamoto et al., 2018).

In adult cases of methyl mercury poisoning the estimated mercury body burden thresholds (mg) at diagnosis for various symptoms were as follows: abnormal sensory perception, about 25 mg (equivalent to a mercury blood concentration of 250 μg/L); ataxia, about 50 mg; articulation disorders, about 90 mg; hearing loss, about 180 mg; death, >200 mg (Sakamoto et al., 2018). In adults, possible health effects of methyl mercury include cardiovascular atherosclerosis, myocardial infarction, heart rate variability, and hypertension (Buchanan et al., 2015; Guallar et al., 2002). Several studies identified a significant positive association between mercury in hair samples and hypertension and between mercury and blood pressure; whereby the exposure dose is an important factor in determining the toxic effects of mercury (Hu et al., 2018). Further studies observed a significant association of higher methyl mercury (but not inorganic mercury) with higher systolic and pulse pressure during pregnancy (Wells et al., 2017). In contrary, higher inorganic mercury in umbilical cord blood, was significantly associated with lower pulse pressure. There was a non-significant trend of higher total mercury with higher systolic blood pressure (Wells et al., 2017).

The toxicity profile of ethyl mercury (i.e. thimerosal, constitute of vaccines) is different from that of methyl mercury. However, in real-life scenarios, co-exposure with ethyl – and methyl mercury in uteri might induce more adverse neurotoxic effects than each agent alone (Bjorklund et al., 2017). Also, there are complex interactions between mercury compounds and other elements, such as i.e. Ag, Pb, Zn, and Cu, resulting in different conditions of metal bioaccumulation in the whole organism and in critical organs. Therefore, the present knowledge on this subject is still incomplete.

2. Some past exposures and long lasting global health threats

2.1. Methyl mercury poisoning, known as Minamata disease

In Minamata (Takaoka et al., 2018) industrial effluents contaminated with mercury have reached lakes from an industrial plant for over 30 years (1932–1968) and led to more than a thousand cases of mercury poisoning. The devastating effects of methyl mercury poisoning became known mainly in the 1950s. Minamata disease - caused by methyl mercury-contaminated effluent released into Minamata Bay by Chisso, Japan's largest chemical manufacturer - was first discovered in Japan in 1956; its name comes from the affected city of Minamata (env.go.jp, 2013; Takaoka et al., 2018; Yorifuji et al., 2013). The analytical study revealed a relationship between the family occupation (fishing) and the disease, and a dose-response relationship between eating fish caught in Minamata Bay and the disease (Yorifuji et al., 2013). Exposure (and its bioaccumulation in fish, shellfish and other sea organisms) subsequently spread not only in Minamata Bay but along the entire coast of Shiranui Sea (see Supplementary tool box 1 for more details on the exposure). The Minamata disease can be considered a typical example of industrial pollution for several reasons. First is the manner of the outbreak. Minamata disease is a form of food poisoning (and indeed carried through the food chain) as a result of environmental pollution (Yorifuji et al., 2013). The disease has also a socio-economic and political dimension, since it was known for years that the disease is attributed to factory effluents but the government took no action to stop contamination or prohibit fish consumption. The Chisso Corporation knew it was discharging methyl mercury and could have known that it was the likely active factor but it chose not to collaborate and even actively hindered research (see Supplementary tool box 1: Minamata story: How the socio-economic interests may influence the devastating spread of environmental contamination and the progress of the disease (Yorifuji et al., 2013).

The Japanese scientist Dr. Masazumi Harada spent most of his career investigating the effects of this disease (Harada, 1978; Harada et al., 2005). He revealed that the Minamata inhabitants' methyl mercury exposure levels peaked in the first five years of the 1950s, the severe symptoms observed at that time included paralysis, coma and death. Sensitivity disorders, mental retardation, cerebellar ataxia, dysarthria, deafness, deformed or functionally impaired limbs, visual and hearing disorders are pathological changes that were included in the medical textbooks as Minamata disease. Most victims were hyperactive, suffered from muscular spasms and uncontrollable slow writhing, and had squints. The important scientific aspect of the Minamata disease is the discovery that methyl mercury is transferred across the placenta to affect (in utero) the development of unborn children, resulting in serious mental and physical problems in later life. Experts missed this at first because of a medical consensus that such transfer across the placenta was impossible.

While mothers usually showed only minor symptoms, the children suffered from paralysis and intelligence disorders, showing that prenatal methyl mercury exposure had stronger effects on fetuses then on their mother. Epidemiologically, the children were coincident with Minamata disease both in timing and location (called congenital Minamata disease related to exposure in utero). Their mothers consumed a large amount of fish and exhibited mild symptoms of the Minamata disease. Two autopsies of infants confirmed methyl mercury intoxication during fetal life (Yorifuji et al., 2013) leading to the congenital form of Minamata disease with cerebral palsy. Histopathological examinations of Japanese fetal-type Minamata disease patients revealed widespread and severe neuronal degeneration in the central nervous system (Sakamoto et al., 2018).

No human or biota samples were collected from the Minamata area during the period of severe methyl mercury pollution. Later, hair samples were taken from the victims of the disease and also from the Minamata population in general. In patients, the maximum mercury level recorded was 705 parts per million (ppm), indicating very heavy exposure. In non-symptomatic Minamata residents the level was 191 ppm (Yorifuji et al., 2009). This compared to an average level of 4 ppm for people living outside the Minamata area. Hair mercury levels above the WHO threshold for adult exposure (50 μg/g) were associated with perioral sensory loss in a dose-response relationship. Recent follow up studies in the Minamata area have shown that the effects of methyl mercury poisoning on human health had spread outside of the central area and could have still been caused until recently (Takaoka et al., 2018). These data revealed that the latency period from exposure of mercury to the onset of symptoms is much longer than previously thought, and that the latency period increases as the exposure levels decreases. They could also confirm a dose-response relationship with the frequency of fish ingestion. Methyl mercury poisoning in adults can cause arthritis, miscarriage, respiratory insufficiency, neurological damage and even death.

2.2. Other historical mercury epidemic poisoning

Later, similar diseases could be attributed to industrial waste water containing mercury from a chemical plant in Ontario, Canada (Harada et al., 2005; thestar, 2016). Between 200 and 600 tons of mercury had entered the water supply. The neurotoxic mercury seeped into the river sediment for more than four decades and reached the food chain of the local Grassy Narrows Indian population for generations. This mercury poisoning of the Grassy Narrows is well documented in the records of Reed Paper's old dry-dene pulp and paper mill. This factory dumped 10 tons of mercury into the Wabigoon English River system between 1962 and 1970. Bacteria living in humid, low-oxygen environments such as marine sediments converted the mercury into its most toxic form, methyl mercury. Methyl mercury then entered the human food chain via fish.

Between 1971 and 1972 in Iraq, widespread consumption of grain coated with an organic mercurial fungicide caused the largest mercury poisoning epidemic ever recorded with a total of 6530 individuals diagnosed with mercury intoxication of which 459 died (WHO, 2010).

Poisonings occur around the world, especially when productions using mercury are moved to places with less regulatory restrictions. In 2001 a thermometer factory was shut down in India after the discovery of a dumpsite containing 7.4 tons stockpile of crushed glass thermometers laced with mercury (theguardian, 2016). In 1984 the thermometer plant had been moved from New York to India over environmental concerns. Between 1984 and 2001 591 employees (and their families) from the now defunct factory were exposed to mercury.

Historical occupational diseases also include erethism mercurialis (hat makers disease or mad hatter syndrome) with symptoms like mental confusion, emotional disturbances, muscular weakness, neurological damage with tremors, and dizziness as a result of using inorganic mercury in the form of mercuric nitrate in the 17th till the late 40ies of the 20th century in the production of hats (Waldron, 1983). Further historical occupations with possible mercury exposures include mirror, watch, and thermometer industries. The psychotic symptoms of mercury poisoning have also been described during the eighteenth century, when mercurial ointments were used in the treatment of syphilis.

3. Current environmental and occupational exposures

Mercury exposures are not equally distributed in the world, due to a large variability of mercury deposition. Therefore, geographical features can influence environmental mercury, and the resulting large variability of environmentally mediated exposures (WHO, 2010). Mercury can enter the environment naturally and from industrial sources, such as industrial mining, the production of chemicals and fertilizers, the disposal of waste and molten metal (see Table 1 for sources of exposure). The largest anthropogenic source of mercury pollution is ASMG in low-income countries (Fig. 1). Exposure risks to mercury arise from numerous different sources and routes of exposure. Above all, in developing nations, particular exposure risks are related to fossil fuel combustion, religious and cultural practices, occupational activities

Table 1
Sources of mercury exposure.

Mercury (Hg) exposure	
Specific exposure groups	Exposure sources
Hg in the atmosphere (Hg pollution in the air) Accidental Hg spills or deliberate misuse	-Use of Hg in industrial processes: coal and other fossil fuel combustion (coal-fired power stations; oil refineries, residential heating systems); gold/other metal- mining; the production of chemicals (i.e. chlor-alkali production or production of vinyl chloride monomer, the main component of PVC), fertilizers, other agricultural products, cement; emissions from industrial or domestic waste incinerators (i.e. e-waste or fluorescent lamps) -Natural Hg emissions and re-emissions: outgassing of the earth's mantle; volcanic activity; geothermal processes; evaporation from soils, evaporation from water bodies and vegetative surfaces; release from forest fires and erosions -Increased Hg release due to climate change: increased wildfires or diminishing sea ice
Hg in the hydrosphere (Hg contaminated fresh water systems and/or marine systems).	-Water contamination with Hg from industrial processes: artisanal and small-scale gold mining, disposal of Hg containing products and domestic waste water, metal production, and releases from industrial installations such as chlor-alkali plants and oil refineries; water discharges from industries utilizing Hg, or mine drainage -Releases of Hg to freshwater environments (rivers and lakes) associated with anthropogenic activities (erosions of soils, runoff from watersheds)
Hg in diet products	Consumption of Hg contaminated fish, shellfish, and marine mammals, poultry, rice
Hg in cosmetic products	Hg in teething powders, lightening skin creams and soaps
Hg in medical products	Hg in pediatric vaccines (with preservative thimerosal which is metabolizing to ethyl mercury); Hg in dental amalgam, laxatives, diuretics, antiseptics, some Ayurvedic medicines
Hg in consumer goods (home and garden products)	Hg in plastic, latex paint additives, batteries, fluorescent lamps, thermometer, bulbs, switches, cosmetics, measuring devices, insecticides, fungicides, pesticides; antiques in the home

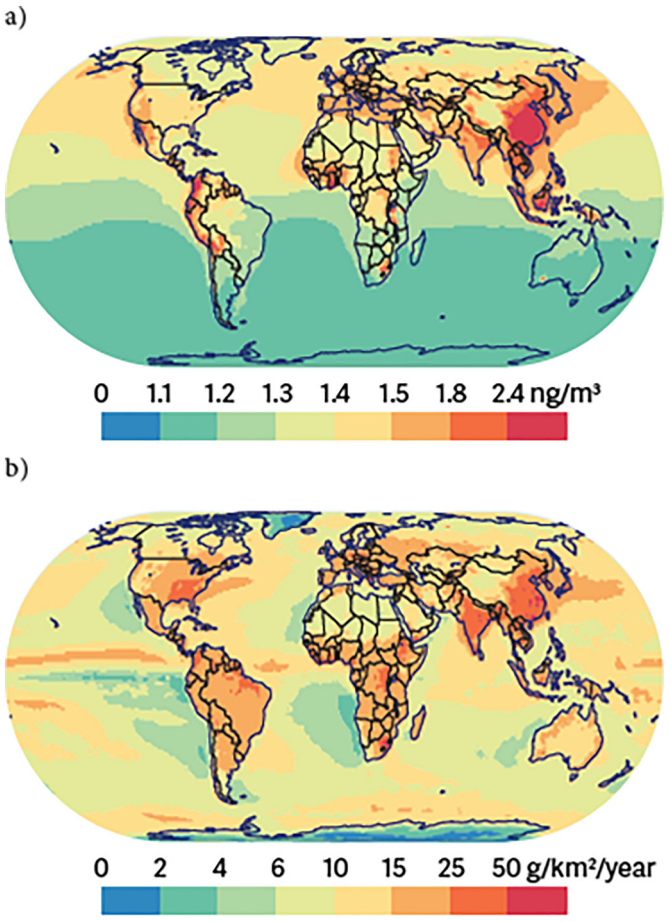

Fig. 1. Global mercury distribution: a) annual mean GEM concentration in ambient air and b) annual total mercury deposition in 2013.
From (UNEP, 2015).

such as gold mining extraction, as well as survival diet exclusively based on fish consumption (Buchanan et al., 2015; Ruggieri et al., 2017; Tsuchiya et al., 2008).

3.1. Emissions of mercury to the atmosphere and global water systems

The emissions of mercury include anthropogenic sources such as fossil fuel combustion, smelting of ores, cement production, waste incineration, and artisanal gold mining (Kobal et al., 2017). Production processes such as those in small gold mining involve the heating of elemental mercury, which results in the release of mercury vapors into the environment (Schmidt, 2012). These mercury vapors are then deposited as dust (Tomiyasu et al., 2017) on the ground or surface water (Gibb and O'Leary, 2014). Aquatic ecosystems are an essential component of the biogeochemical cycle of mercury, as inorganic mercury can be converted to toxic methyl mercury in these environments and reemissions of elemental mercury rival anthropogenic mercury releases on a global scale (Kocman et al., 2017) to freshwater environments (rivers and lakes). Adsorption capacity of mercury in the Mississippi River deltaic freshwater marsh soil was found to be significantly influenced by potential environmental changes implicating that such factors should be considered in order to manage the risks associated with mercury in freshwater wetlands for responding to future climate change scenarios (Park et al., 2018). Extreme climate events like droughts increase the trophic transfer of contaminants and net methylation of mercury (Azevedo et al., 2018).

3.2. Biogeochemical cycling of mercury and impact of climate change

Terrestrial vegetation plays an important role in the biogeochemical cycling of mercury and is considered a significant reservoir for atmospheric mercury (Kumar et al., 2018). Wildfires, through the burning of biomass, can effectively mobilize mercury stored in terrestrial ecosystems and lead to massive emissions of mercury and other pollutants into the atmosphere. Since the wildfires are increasing under conditions of global climate change, multiple studies have estimated mercury wildfire emissions at global and regional scales, developing wildfire emission inventories for mercury based on CO or CO_2 emission inventories by applying fixed emission ratios between mercury and CO/CO_2 (Kumar et al., 2018). Africa (43.8%), Eurasia (31%) and South America (16.6%) are found to be the major sources of mercury wildfire emissions in the 2000s (1998–2002 average). While 2000–2050 climate change and land cover could increase wildfire emissions, projected changes in land use by 2050 could decrease the global mercury emissions by continued anthropogenic destruction of natural vegetation in order to support agricultural development.

Wildfire emissions of mercury in the boreal regions are predicted to increase in response to the 2000–2050 changes in climate, land cover and anthropogenic mercury emissions which could have significant implications for mercury deposition to the Arctic (Kumar et al., 2018).

Diminishing sea ice, due to climate change, could also cause more mercury evasion from the ocean to the air becoming a health risk to ecosystems and human beings (Wang et al., 2017). Atmospheric mobilization and exchange at the air-water interface are important processes in biogeochemical cycling of mercury at the Earth's surface. Enhanced mercury concentrations in the seas near the Antarctic and even contamination in Antarctic biotopes' have been observed. Evidence is emerging that the sea ice environment can play an important role in the distribution, transport and transformation of mercury in the Antarctic or Arctic (Wang et al., 2017).

To evaluate the impacts of natural and anthropogenic perturbations on mercury exposure risk, we must consider the complex array of atmospheric, hydrological, biological, ecological, and geochemical processes that control mercury transport and transformation to methyl mercury in the environment (Hsu-Kim et al., 2018). For example, recently deposited, transported, or mineralized mercury tends to be more reactive towards methylation and bioaccumulation than “old” mercury that has aged in place in sediments and soil (Hsu-Kim et al., 2018). Mercury directly deposited to surface waters from the atmosphere has been observed to methylate and bioaccumulate in aquatic food webs relatively quickly (e.g., within months to a year), while mercury deposited to upland terrain generally requires much more time (a decade or more) for subsequent impact on pelagic food chains. Identification of the chemical forms (or aging states) of mercury and methyl mercury that enter surface waters can help guide policies that prioritize reductions of certain sources, or perhaps assign value terms to individual sources as a basis for economic incentives or trading programs for discharge permits (Hsu-Kim et al., 2018).

3.3. Exposure via diet or home products

Organic mercury, the most hazardous and most frequent form of mercury exposure (methyl-/ethyl mercury), is frequently detected in fish, poultry, insecticides, fungicides, pesticides (Bjorklund et al., 2017; Crowe et al., 2017).

In some regions of the world such as China, methyl mercury exposure via a rice-based diet is an increasing risk factor (WHO, 2010). When analyzing potentially important determinants of the methyl mercury exposure in the industrialized country, like the US, Buchanan et al. found some ethnic and cultural attributes like Asian diets, being born outside of the US and higher family income (Buchanan et al., 2015). Some traditional practices employed for cultural and religious purposes can be associated with mercury exposures. A number of practices occur

worldwide that utilize mercury, including Santeria (Afro-Hispanic tradition), Espiritsmo (Puerto Rican), Voodoo (Afro-Haitian), Palo Mayombe (Caribbean), Candomble (Afro-Brazilian), and various forms of Ayurvedic medicine (WHO, 2010). Some of these traditional practices are becoming popular with trans global tourism and internet. However, the exact extent of mercury use through these practices is largely unknown (Budnik et al., 2016).

Concerns about human life exposure are mostly related to methyl mercury that accumulates in fish and other food. Assessment of mercury in raw food samples from open markets in Kinshasa (Democratic Republic of Congo) and Johannesburg (South Africa)showed mercury values of 1.53 ± 0.1 to 2.94 ± 0.23 mg/kg (Nuapia et al., 2018). Average mercury values in raw foods collected from Johannesburg market were significantly higher ($p < 0.05$) than those from the Kinshasa market. The fish samples from Kinshasa showed lower mercury concentration as compared to those from Johannesburg, the latter being higher than the permitted mercury limit of 0.5 mg/kg (0.5 μg/g) set by the European Commission. These concentrations were also higher than those found in fish sold in Palestine. The levels in Johannesburg were exceeding the recommended maximum acceptable limit proposed by the Joint FAO/WHO Expert Committee on Food and by the US EPA/FDA (0.46 μg/g, highest allowable average mercury concentration in fish, when eating two servings per week) (EPA, 2018; European-Commission, 2018).

Bio-accumulates of methyl mercury in aquatic food chains and the capacity to cross the blood–brain barrier make this organic mercury compound more disturbing than inorganic mercury (Bjorklund et al., 2017). It is generally found that about 80–100% of total mercury in fish muscle is methyl mercury; in seafood other than fish, methyl mercury typically comprises 50–80% of total mercury. In other foods, mercury is presumed to be present as inorganic mercury. Several studies have measured the amounts of mercury found in fish muscle tissue, i.e. of samples of swordfish (*Xiphias gladius*) found in different FAO fishing areas and imported in Italy between 2014 and 2017 (Esposito et al., 2018). Mercury intake values were calculated and compared with those of the Provisional Tolerable Daily Intake (PTDI) (0.57 μg/kg b.w./day) as fixed by the Food and Agriculture Organization/World Health Organization (FAO/WHO). The estimated values were lower than the PTDI in adults (0.40 μg/kg b.w./day) but not in children (0.97 μg/kg b.w./day), and therefore are considered to pose an alert for children with the present fish consumption volume. However it has to be pointed out that many studies do not measure methyl mercury, but rather total mercury. This leaves a certain degree of uncertainty. Also the position of the sea fish in the food chain and the biomagnifications of methyl mercury through the food chain lead to significantly higher values. Studies have shown that mercury concentrations were higher in Mediterranean than Atlantic fish (Junque et al., 2018). Extrapolation of the observed mercury concentrations in Mediterranean fish to Provisional Tolerable Weekly Intakes (PTWIs) showed higher intakes than the thresholds recommended by EFSA for adults and children, 110% and 140%, respectively. The estimated PTWIs for methyl mercury corresponded to 310% and 400% of the recommended threshold values. Human intervention studies in central Europe with 67 volunteers showed mercury intake from fish meals. Total mercury was analyzed in blood and hair samples as well as in muscular tissues of fish. The mean of the estimated weekly intake (EWI) was estimated at 0.62 μg/kg bw/week in the range 0.36–0.96 μg/kg body weight (bw)/week through the consumption of 4 edible marine fish species every day (for 10 days) by the participants. The mercury intake in the volunteers in the intervention study accounted for 38.6% of the Provisional Tolerable Weekly Intake (PTWI) (1.6 μg/kg bw, weekly) value. The average concentration of mercury in the selected fish after heat treatment did not exceed the maximum permitted concentrations for methyl mercury (MPCs = 0.5 mg/kg wet weight) in food set by the European Commission (Kuras et al., 2017).

It has to be noted that, climate change increases exposure and bioaccumulation of pollutants, such as mercury in marine organisms, posing substantial toxicological risks (Alava et al., 2018). The level of amplification increases with higher carbon emission scenario for methyl mercury, leading to modifications of food web dynamics between different levels of climate change (Alava et al., 2018).

3.4. Old and new industries and products

While mercury was phased out from thermometers used in industry and laboratory (EPA, 2017), new industries, with new potential mercury exposures are emerging like tube light, compact fluorescent lamp and mercury vapor lamp industries. Artisanal and small-scale gold mining represents the single largest source, followed by disposal of mercury-containing products and domestic waste water, metal production, and releases from industrial installations such as chlor-alkali plants and oil refineries (Kocman et al., 2017).

Destruction and recycling of fluorescent lamps may present a risk for adverse health effects from mercury exposure to workers in fluorescent lamps recycling facilities, with potential for take-home exposure and environmental contamination. American studies (Maine Compact Fluorescent Lamp Study) conducted by the Maine Department of Environmental Protection in February 2008 showed that when a compact fluorescent lamp is destroyed, mercury can be released into the air in high concentrations (maine.gov, 2008). The German Federal Environment Agency (UBA) commissioned a pilot study at the Fraunhofer Wilhelm-Klauditz-Institute (WKI) to verify these results and check the hazard situation of modern compact fluorescent lamps with low mercury content. The WKI is currently carrying out follow-up studies with different types of energy-saving lamps in test chambers and offices, taking into account ventilation and clean-up scenarios. The results were assessed on the basis of the mercury guideline values from the ad hoc Working Group “Indoor Indoor Air Hygiene Guidelines” of the Indoor Air Hygiene Commission of UBA and the Supreme State Health Authorities. The results of the experiments in the test chamber showed a significant exceedance, indicating that above the German environmental air limit value RW II of 0.35 μg/m^3, indicating that immediate action is required (UBA, 2016).

ASMG represents the livelihood of at least 10–15 million people in 70 countries (including possibly as many as at least 3 million women and children) and is based on the extraction of this precious metal using elemental mercury (Gibb and O'Leary, 2014). Many of the workers and their families are exposed to high levels of exposure to elemental mercury, not only at work, but also at home and in their communities (Gibb and O'Leary, 2014; Yard et al., 2012).

Waste containing elemental mercury (i.e. batteries, fluorescent lamps, thermometer, electrical switches) can cause further environmental damage if it is not protected from wind and rain. Mine waste and seepage water often end up in rivers, lakes and streams and then pose a serious health risk for years (Rice et al., 2014). Coal combustion is one of the largest contemporary sources of anthropogenic mercury (Giang et al., 2015; Liang et al., 2015; Streets et al., 2018). 71% of the total, were directly emitted to the atmosphere, mostly from the industrial (45%) and power generation (36%) sectors, while the remainder is disposed of to land and water bodies (Streets et al., 2018). A further important source of exposure is the recycling of industrial waste (Laborde et al., 2015). Approximately 50 million tons of electrical and electronic waste (e-waste) is generated annually and is known to contain numerous environmental toxicants, including mercury. E-waste may pose significant health risks to children, especially child workers (see below), who may be confronted with hazardous substances through take-home exposures and home-based e-recycling workshops (Laborde et al., 2015).

Production of mercury accounts for 27% of cumulative mercury releases to the environment, followed by silver production (24%) and chemicals manufacturing (12%). North America (30%), Europe (27%), and Asia (16%) have experienced the largest releases (Streets et al., 2017). Beside the atmospheric emissions from “byproduct” sectors

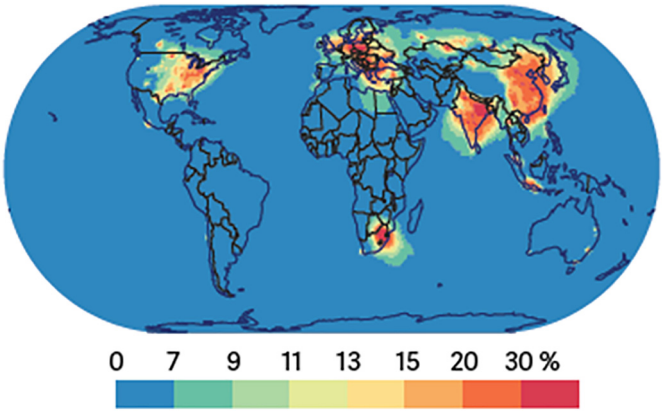

Fig. 2. Mercury deposition in 2013: relative contribution of industrial/commercial mercury use.
From (UNEP, 2015).

(e.g., fossil fuel combustion), other commercial/industrial emissions release mercury from chlor-alkali production, waste incineration, and mining (Horowitz et al., 2014). Commercial mercury (Fig. 2) use peaked in 1970 and has declined sharply since its release (air: 20%; water: 30%; soil: 30%; landfills: 20%), however has been sequestered in landfills and benthic sediments (global burial in ocean margin sediments) (Horowitz et al., 2014).

Power plants generate more airborne mercury pollution than all other industrial sources combined. In the US, two-thirds of all airborne mercury pollution in the United States came from the smoke stacks of coal-fired power plants, based on the data from the Toxics Release Inventory (TRI), U.S. Environmental Protection Agency's (EPA) (Madsen and Randall, 2011).

Of further concern is the continued use of mercury in some production processes: in the production of acetaldehyde (the source of the contamination at Minamata) or the use of mercury in the production of vinyl chloride monomer, the main component of PVC plastic (IPEN, 2013). Mercury is used in pesticides and certain batteries, bulbs, switches, cosmetics, measuring devices and in dental amalgam. Mercury intoxication may have further multiple exposure sources (e.g., use of mercury-containing skin creams and soaps, fish consumption by themselves or by pregnant women, use of pediatric vaccines (with preservative thimerosal which quickly metabolizes to ethyl mercury) (Budnik et al., 2016; Hermann et al., 2015). Inorganic mercury salts have been found in thermostats, thermometers, laxatives, cosmetic products, latex paint additives, teething powders, dental amalgam, diuretics, and antiseptics (Ozuah, 2000).

4. Special impact of mercury exposure on children's health

As children are different from adults in several respects, including differences in metabolism (potentially signifying less effective detoxification and physiological elimination of contaminants), diets, patterns of behavior, growth and changes of organ systems and functions, this special vulnerable group should be considered separately. It is known that specific windows exist in the prenatal time span in which metals show a particularly high degree of toxicity (Bjorklund et al., 2017).

Generally, mercury exposure may start at the point of conception. Beyond the critical time of gestation it continues throughout the stages of infancy, childhood, and adolescence. (Laborde et al., 2015; Ruggieri et al., 2017; WHO, 2010). During prenatal exposure, the sources of exposure for pregnant women are also sources of fetal exposure, and, among various factors, special emphasis has been addressed to mother's dietary intake of fish, shell-fish or marine mammals (the last one, particularly, in the Arctic and sub-Arctic populations) (Gibicar et al., 2006; Ruggieri et al., 2017). Throughout the developed and developing world, children face mercury exposure risks from numerous different sources as well to multiple different species of mercury both in utero and during early development. Pregnant women who eat methyl mercury-contaminated fish endanger the development of the peripheral and central nervous system of the fetus; this can lead to mental retardation, delayed development, speech disorders, seizures and impaired memory. Analysis of the US NHANES data generated between 2011 and 2012 showed that Asian women of child bearing age (WCBA) continue to have increased methyl mercury exposure from fish consumption (Buchanan et al., 2015), A pathway of concern for pregnant women is also represented by mercury vapors released from maternal dental amalgams (Lygre et al., 2016). The risk for WCBA and fetus may increase with cumulative exposure i.e. from fish consumption (methyl mercury) and thimerosal containing vaccines (ethyl mercury), which in some cases may result in differential neurological effects (Dórea, 2017).

Maternal mercury concentrations correlated with the levels of mercury in cord blood and in children up to age 60 months in a study by Jeong et al. (2017). This correlation may be due to the high transplacental transmission of these metals and the shared living environment including environmental exposure, food consumption, and lifestyle. Total mercury concentration was highest in cord blood, and gradually decreased with child age. Since maternal exposure to mercury could produce damage on neuro-developmental systems (behavioral, cognitive patterns and motor skills) during pregnancy, it may affect the quality of life in adolescents and adults (Ruggieri et al., 2017). Children chronically exposed to methyl mercury can develop acrodynia, characterized by redness and severe pain in the extremities.

Later in life, the immune and reproduction systems could be affected by the persistent prenatal exposure to mercury (Grandjean and White, 2002). In terms of health risks, the interactions between mercury-induced immune toxicity and the inadequate hygienic conditions in many ASGM communities may place children at risk for infectious diseases, like i.e. increased risks of malaria infection (Silbergeld et al., 2005). Children exposures to metallic mercury are extensive in artisanal gold mining, and highly neurotoxic methyl mercury from metallic mercury that enters streams and rivers is a further hazardous consequence of ASGM (Grandjean et al., 1999). While the exact number of people participating in ASGM is difficult to calculate, it is estimated that 10 to 15 million individuals directly participate worldwide, including up to one million children (Veiga and Baker, 2004). ASGM are distributed in central and south Africa (the Sahel Region of Burkina Faso and Niger, Ghana, Zimbabwe, Tanzania), central and South America (Bolivia, Ecuador and Peru, thought Amazonian regions) and in South East Asia (especially China) (UNEP, 2015). Many families transition their children from school to the mines when they reach 8–12 years of age. Children commonly play a major role in mercury amalgamation since it does not require immense strength. During the amalgamation process, metallic mercury may be absorbed through the skin. Children not actively participating in ASGM still face exposure to vaporized mercury from family members burning amalgam in the home or in their proximity or to spending time close to ASGM locations where family members are working (Bose-O'Reilly, 2008). Children who live in nearby communities may also be chronically exposed to mercury via ingestion of contaminated fish or rice or breast milk from their mothers, who may also work in or be secondarily exposed to mercury from this activity. Children whose parents work as miners may be exposed to mercury residue on the parents clothing, hair, and skin. Additionally, in a worst case scenario, as much as 95% of mercury used in ASGM can be released into the environment, constituting danger to human health (Veiga and Baker, 2004).

Three long term epidemiological/developmental studies were conducted in the Seychelles Islands, the Faroe Islands, and New Zealand. The studies identified methyl mercury-related developmental neurotoxicity, yielded scant evidence of impairment related to in utero methyl mercury exposure and found dose-related effects on a number

of neuropsychological endpoints (for further references see: Grandjean et al. (2012), Grandjean and White (2002)).

5. Incorporation routes and health hazards of organic and elemental mercury

The toxicity of mercury compounds depends on the exposure pathway: ingestion, inhalation, trans-dermal, and trans-placental (Ruggieri et al., 2017). Also nutritional background can influence the uptake and distribution of mercury species while sex and genetic background have been shown to influence the overall body burden of mercury in both epidemiological and experimental studies (Chapman and Chan, 2000). The individual can incorporate mercury by inhalation, ingestion and skin contact (Crowe et al., 2017) and the fetus can be exposed in utero. Trans placental exposure is the most dangerous, as the fetal brain is very sensitive. Neurodevelopmental effects of in utero mercury exposure include mental retardation, congenital malformations, vision and hearing loss, delayed development, and language disorders.

The most direct route of mercury pollution is the inhalation of mercury vapors. These can reach the brain and cause permanent damage. The intake of methyl mercury, a powerful neurotoxin, is mostly due to the consumption of contaminated food such as fish and seafood. After ingestion via the digestive tract, methyl mercury reaches the brain where it accumulates over a long period of time. In pregnant women, it is incorporated into the fetal brain and other tissues. Studies have shown that farm animals can absorb large amounts of mercury in contaminated pastures, which in turn leads to contamination of human food.

Other common exposure pathways include absorption through the skin and breast feeding from women exposed to mercury. Skin lightening products contain inorganic mercury aimed to inhibit production of the skin pigment melanin in epidermal melanocytes, as active ingredient. Skin-lightening products have a indicative role in the treatment of hyper pigmentation disorders by dermatologists. However, such products are also commonly used in a number of African, Asian and Latin American countries or in the Middle East to produce a general cosmetic lightening of the skin. It has to be noted, that mercury-containing skin-lightening products do not always list mercury compounds as an ingredient (Dlova et al., 2012), which may lead to numerous undiscovered exposures. A case report by (Hermann et al., 2015) showed a child exposed to inorganic mercury through breast milk and skin contact with bleaching crème (through bed linen). The boy suffered from renal artery hypertension (classified as reno-parenchymatous hypertension). At age 2.5, the continuous mercury exposure, lead ultimately to progressive unrest, developmental regression, and self-injurious behavior by excessive scratching of hands and feet due to intractable pruritus. The patient lost not only his teeth, but also his previously acquired ability to speak.

Occupational handling of mercury is the most dangerous hazard due to frequent or prolonged direct contact. A study has shown that more than half of Indonesian gold miners develop chronic mercury intoxication, with even low exposed individuals such as those in mineral processing and nearby high concentrations of mercury (Bose-O'Reilly et al., 2010a). Infants who are breastfed were shown to be particularly at risk of developing developmental disorders (Hermann et al., 2015). Most frequently, health problems are reported among workers in the small-scale gold mining industry, such as tremor, ataxia, memory problems and visual impairment (Bose-O'Reilly et al., 2010b). Additional symptoms include headache, mood swings, muscle weakness, insomnia, dizziness, mucosal irritation in the mouth, fatigue, walking difficulties, persistent cough, chest pain and rhinitis (Doering et al., 2016).

6. Patho-physiological mode of action

Mercury compounds cause toxic action in the body by numerous mechanisms. Mercury can cross the blood-brain barrier and is rapidly oxidized to ionic Hg^{2+} intracellular (Bjorklund et al., 2017), which is retained in the brain cells for years (Berlin et al., 2015). Molecular and cellular effects of organic mercury in the nervous system have been described in various studies and have suggested that Hg^{2+} may play a role after exposure to ethyl mercury or methyl mercury and that occurrence of Hg^{2+} in neurons results from breakdown of organic mercury in glial cells (Bjorklund et al., 2017). It was further found that the levels of Hg^{2+} after ethyl mercury exposure were higher than after methyl mercury exposure, while damaged granular layer was observed only after methyl mercury exposure. Therefore, it was proposed that the demethylation action or Hg^{2+} could not be the basic promoter responsible for methyl mercury neurotoxicity (Bjorklund et al., 2017). Since it has been observed that methyl mercury present in glial cells, could subsequently be detected in neurons in the symptomatic phase, the demethylation might occur in the glial cells after the mercury movement to neurons (Syversen and Kaur, 2012). Also, both organic and inorganic mercury (CH_3Hg^+ and Hg^{2+}) exhibit strong affinity to thiol groups that have been demonstrated to play a significant role in the toxic mechanism of mercury and its compounds (Bjorklund et al., 2017; Risher and Tucker, 2017). Oxidative stress, damaged calcium homeostasis, as well as the glutamate homeostasis changes reported in numerous studies are likely to be involved in the sub-cellular neurotoxicity of methyl mercury (Bjorklund et al., 2017). Another mode of action is by blocking calcium-binding proteins including calmodulin interfering with cellular processes by substituting Calcium on essential constituents (Bjorklund et al., 2017) and inducing neuro-inflammatory changes (Ray and Lahiri, 2009). Methyl mercury could induce adverse effects on cytoskeletal proteins (microtubules) and cytoskeleton-regulating proteins (Rho family proteins), causing disturbances in neuronal migration and differentiation (dos Santos et al., 2016). Methyl mercury reveals a high affinity for SH-groups of tubulin (Bjorklund et al., 2017), which may lead to the depolymerization and derangement of cerebral microtubules (Carratù and Signorile, 2015). Methyl mercury can also attenuate expression of microtubule-associated protein-2 (MAP-2) in neurons and lead to hyper-phosphorylation of tau. Also, it could induce deficits in hippocampus dependent spatial learning and memory during adolescence apparently due to inhibited development of dentate gyrus neurons (Tian et al., 2016). The intracellular low-molecular-weight thiol glutathione (GSH) induces protective effects, i.e., through its role as a cofactor for the glutathione peroxidase seleno enzymes. Astrocytes, notably the cortical astrocytes of brain cells, have a high capacity for GSH synthesis that may explain their relative resistance against mercury toxicity (Bjorklund et al., 2017). Recent literature suggests that methyl mercury leads to elevated generation of ROS that may either reduce GSH levels or initiate an adaptive response to oxidative stress by increasing GSH levels.

7. Biomarker of mercury exposure: human biomonitoring

Defining safe levels of mercury continues to be an active research area. The toxicity of mercury compounds depends on the exposure pathway: ingestion, inhalation, trans-dermal, and trans-placental (Ruggieri et al., 2017). Though it is clear that adverse health effects of mercury occur even at low exposure doses, it is not clear whether, or to what extent, toxicity from the various forms of mercury is cumulative and remains the subject for future studies.

Safe levels of mercury in food have been provided by both the European Commission and EPA/FDA (EPA, 2018; European-Commission, 2018), The minimal risk levels for chronic inhalative mercury exposure have been determined at 0.0002 mg/m^3 level, while chronic oral exposure to methyl mercury is defined at: 0.0003 mg/kg/day (CDC, 2018b). However, for the estimation of the internal dose of mercury and its risks to human health, it is essential to perform human biomonitoring. Only human biomonitoring can reveal whether and to what extent mercury species were really taken up by humans from the environment or food (CDC, 2018c). This information cannot be provided by

ambient monitoring of air, water, or other environmental samples. Human biomonitoring of mercury is also a useful tool to support environment and health policy-making, because it can provide quantitative information regarding the actual mercury exposure of a population and support the evaluation of preventive actions.

7.1. Human biomonitoring approach need information on exposure scenarios

Interpretation of mercury exposure biomarkers (within the human monitoring) requires knowledge of exposure scenarios. Boerleider et al. provided an overview of the different human biomonitoring approaches for long- and short-term exposure to mercury and methyl mercury in children and adults by discussing: (1) the appropriate selection of biomarkers for assessment of different mercury exposures, and (2) the advantages and limitations of the different biological matrices used in human biomonitoring for mercury exposure (Boerleider et al., 2017). While total blood mercury is mainly a measure of methyl mercury exposure, mercury in the urine is a measure of inorganic mercury exposure (CDC, 2018c). By measuring mercury in blood and in urine, the amounts of mercury that has entered people's bodies can be estimated. Nutritional background can influence the uptake and distribution of mercury species and thus the human biomonitoring values, while sex and genetic background have been shown to influence the overall body burden of mercury in both epidemiological and experimental studies (Chapman and Chan, 2000).

Note that, for the interpretation of the human biomonitoring data, there is important to know the difference between reference values and health based limit values. The reference values (RV) are purely statistically defined values, which have no health significance per se (UBA, 2018). Where possible, the reference values are determined on a suitable reference population, such as the Environmental Survey. Among other things, they allow the description of the actual state (background exposure burden) in a specific population group with or without a recognizable specific exposure at the time of the examination. The human biomonitoring (HBM) values (HBM-I and -II), on the other hand, are derived on the basis of toxicological and epidemiological studies. To date, the derivation of toxicologically- induced HBM values has traditionally been based on studies demonstrating an association between the concentration of a substance or its metabolites in human body fluids and the occurrence of adverse effects. While, the HBM I value is to be regarded as a test or control value, the negative health effects cannot be excluded when the mercury levels are between HBM I and HBM II. The HBM II value corresponds to the concentration of a substance in a body medium which, if exceeded by the current assessment by the HBM Commission, may cause a health impairment that is considered relevant, so that there is an acute need to reduce the burden and environmental medical care (medical advice needed). The HBM II value must therefore be considered as an intervention and measure value (i.e. in case of mercury to initiate a chelate-binding therapy). The use of HBM values by the physician, should also take into account the exposure history, symptoms and temporal relationships (UBA, 2018). See Table 2 for current HBM-limit values and examples of the current RVs.

7.2. Hair analyses provide information on exposure to methyl mercury over time periods

For hair analysis, total mercury is generally accepted as a good proxy for methyl mercury exposure, while it is not an indicating biomarker for ethyl mercury exposure assessment (Castano et al., 2015). Hair mercury concentration as a biomarker of methyl mercury exposure can provide information over a definable period of time, based upon sequential analyses of hair segments, to represent both the magnitude and timing of past exposure. In the US, the mean hair mercury concentration among women 16–49 years old in a statistically representative sample of the national population in that category was reported to be 0.47 μg/g (McDowell et al., 2004).

Within the European project DEMOCOPHES, 1799 mother–child pairs from 17 European countries were analyzed using a strictly harmonized protocol for mercury analysis. Parallel, harmonized questionnaires on dietary habits provided information on consumption patterns of fish and marine products. There was a strong correlation ($r = 0.72$) in hair mercury concentration between mother and child in the same family, which indicates that they have a similar exposure situation (Castano et al., 2015). The data from NHANES show US reference value of 0.41 μg/g

Table 2
Human biomonitoring: HBM limit values and the reference values (RV).
Sources German HBM/RV values: UBA (UBA, 2018); US RV values: CDC (CDC, 2018a,b,c).

Parameter	Dimension	Health based limit values		RV 95th percentile (95% conf. interval)		Age group
		HBM I[a]	HBM II[a]	RV German population	RV US population	
Total blood mercury	μg/L	5	15	2.0 (18–69 y)[b]	4.66 (20 y+) 3.95 f (20 y+) 4.67 m (20 y+)	Adults
				0.8 (3–14 y)[b]	1.06 (1–5 y)	Children
Blood methyl mercury	μg/L			n.d.	4.92 (20 y+) 3.91 f (20 y+) 3.99 m (20 y+)	Adults
				n.d.	1.11 (1–5 y)	Children
Blood ethyl mercury	μg/L			n.d.	<LOD (20 y+)	Adults
				n.d.	<LOD (1–5 y)	Children
Blood inorganic mercury	μg/L			n.d.	0.56 (20 y+)	Adults
				n.d.	<LOD (1–5 y)	Children
Urinary mercury	μg/L	7	25	1.0 (18–69 y)[c]	1.76 (20 y+) 1.75 f (20 y+) 1.55 m (20 y+)	Adults
				0.4 (3–14 y)[c]	1.37 (6–11 y)	Children
Urinary mercury (creatinine corrected)	μg/g creatinine	5	20		1.76 (20 y+) 1.83 f (20 y+) 1.31 m (20 y+)	Adults
					1.11 (6–11 y)	Children

n.d.: not determined.
f = female; m = male.
[a] Adults and children.
[b] Max. 3 fish servings per month.
[c] Without amalgam.

hair for children (1–5); the Czech Republic data show reference values of 0.60 μg/g for children (8–10), while the adolescents (14–16) show values of 0.474 μg/g for Belgium. At present, there are no official German HBM-values for mercury in hair due to the lack of representative studies. Also according to UBA, external quality assurance for mercury analysis in hair is not offered at present (UBA, 2018). WHO proposed an initial screening level for further action of 2 μg/g hair (Step 2 in the Risk Manager's decision tree) (Sheehan et al., 2014).

In a study by (Arrifano et al., 2018) methyl mercury and total mercury contents were analyzed in hair samples of Amazonian population near Tucuruí Dam. The median level of total mercury in hair was above the safe limit (by the World Health Organization), with values up to 75 μg/g (about 90% as methyl mercury). A large percentage of the participants (57% and 30%) showed high concentrations of total mercury (≥10 μg/g and ≥20 μg/g, respectively), with a median value of 12.0 μg/g. These are among the highest concentrations ever detected in populations living near Amazonian dams. The area analyzed is not highly influenced by gold mining as a source of mercury contamination. Still, it was recently noted that one of the most consumed fishes (*Cichla* sp.) is possibly contaminated with methyl mercury (Arrifano et al., 2018).

7.3. Total blood mercury show both organic and inorganic mercury levels

Unlike hair, total blood mercury levels also include inorganic mercury, which may be of importance in certain contexts. It is generally considered the appropriate indicator of the absorbed dose. Analyses of data collected as part of the US National Health and Nutrition Examination Survey in 2005 and 2006 showed that the 95th percentile for mercury in blood was 1.43 μg/L for children 1–5 years of age (n = 968) (Caldwell et al., 2009). Mortensen et al. have calculated reference ranges and examined demographic factors associated with specific mercury species concentrations and the ratio of methyl mercury to total mercury (Mortensen et al., 2014). The authors conducted several multiple regression analyses to examine factors associated with MeHg concentrations and emphasized that despite the public health and toxicologic interest in methyl mercury and ethyl mercury, these mercury species have been technically difficult to measure in large population studies. Of the overall U.S. population, 3.05% (95% CI 1.77, 4.87) had methyl mercury concentrations >5.8 μg/L (a value that corresponds to the U.S. EPA reference dose). The prevalence was highest in Asians at 15.85% (95% CI 11.85, 20.56), increased with age, reaching a maximum of 9.26% (3.03, 20.42) at ages 60–69 years. Females 16–44 years old had a 1.76% (0.82–3.28) prevalence of methyl mercury concentrations >5.8 μg/L. Asians, males, older individuals, and adults with greater educational attainment had higher methyl mercury concentrations. The ratio of methyl mercury to total mercury varied with racial/ethnic group, increased with age, and was nonlinear. U.S. population reference values for methyl mercury and the ratio of methyl mercury to total mercury can assist in more precise assessment of public health risk from methyl mercury consumed in seafood (Mortensen et al., 2014). It is generally believed that absorption of ingested methyl mercury is high and not likely to vary a great deal.

There is no sufficient information on mercury compartmentalization and the half-lives for individual mercury species in blood. Animal data show that mercury is highly resorbed by inhalation (80%), as well as from the gastrointestinal tract and the skin. It binds easily to the SH-groups of the proteins, peptides or amino acids and is associated primarily with erythrocytes in blood. This binding is very strong, and therefore the distribution of these compounds for other tissues occurs slowly. Methyl mercury compounds are excreted for about 90% by the bile and the liver to the feces. Smaller amounts are excreted by the kidneys. The clearance half-lives for methyl mercury range from 32 to 189 days (depending on the exposure concentration). In the case of mass poisoning with methyl mercury in Iraq the mercury half-life was shown to range from 110 to 190 days. According to Pichichero et al. the blood mercury half-life in children after thimerosal exposure was calculated to be 3.7 days, which is considerably shorter than the half-life of methyl mercury (Pichichero et al., 2008). The earlier mentioned 2 year old boy with mercury intoxication after exposure trough breast feeding and contact with bleaching crème containing 829 μg/g mercury showed elevated blood mercury levels (45 μg/L). After 180 days these were still above the reference values for children, but below the HMB limit values (Hermann et al., 2015).

Except for certain exposure scenarios (i.e. to determine exposure pathway), the measurement of mercury in breast milk is less suitable for mercury exposure assessment. Mercury appears in human milk at smaller concentrations than lipid-soluble chemicals and is about 20% of the level found in blood from the same person (Massart et al., 2008).

7.4. Urinary mercury as a biomarker for the exposure from inorganic mercury

Urinary mercury concentrations are widely used as a biomarker of mercury exposure from elemental or inorganic mercury, like small scale gold mining, mercury found in products (i.e. fluorescent lamps). Mercury correlates well with industrial air pollution. In 79 e-waste workers' in Thailand, urinary mercury levels were 11.60 ± 5.23 μg/g creatinine (range, 2.00 to 26.00 μg/g creatinine) and the mean airborne mercury levels were 17.00 ± 0.50 μg/m^3 (range, 3.00 to 29.00 μg/m^3). The urinary and airborne mercury levels were significantly correlated ($r = 0.552$, $p < 0.001$). (Decharat, 2018). The median concentration of mercury in urine in 616 participants from an area with industrial pollution in China, was 9.14 μg/L (IQR: 5.56–12.52 μg/L; ranging 0.16–71.35 μg/L). A total of 42.7% of the participants were beyond normal level for non-occupational exposure according to the criterion of mercury poisoning (≥10 μg/L) (Lu et al., 2018). This non-occupational environmental exposure to mercury pollution in reproductive-aged men in China was associated with altered DNA methylation outcomes at imprinting gene H19 in sperm, implicating the susceptibility of the developing sperm for environmental insults (Lu et al., 2018).

Mercury exposure levels in the Wanshan mercury mining area were analyzed by Du et al. (2016). The total mercury concentrations of the hair samples of the participants were inversely proportional to the distance of the home dwelling from the mine waste. Urinary mercury was higher in the children urines than in adults ones, which suggests a higher inorganic exposure for children than for adults in the mining area. Inorganic mercury contained in urine primarily originated from: (1) inhalation of contaminated air; (2) ingestion of contaminated vegetables with a high ratio of inorganic mercury or, (3) ingestion of soil (Du et al., 2016).

Urine mercury concentrations and individual soil measurements were also applied for risk assessment of children and mothers in an area with recently detected mercury-contaminations in Switzerland (Imo et al., 2018a). Mothers and children had geometric means of 0.22 μg Hg/g creatinine in urine (95th percentile (P95) = 0.85 μg Hg/g) and 0.16 μg Hg/g (P95 = 0.56 μg Hg/g), respectively. No evidence for an association between mercury values in soil and those in human specimens was found (Imo et al., 2018b).

7.5. Human mercury biomonitoring, as a valuable approach in primary prevention

As for all human biomonitoring studies it is necessary to consider how well the biomarker of internal dose (i.e., the concentration of mercury in hair, blood, etc.) correlates with the external exposure. Since early health effects are often not well detected the determination of the internal dose (total mercury in blood) trough human biomonitoring is a valuable approach in primary prevention (Cullen et al., 2014; Horvat et al., 2003). Bearing this in mind, properly perform human biomonitoring studies may enhance public health affords to reduce exposures in exposed subpopulations and in the general population. Such population-based

biomonitoring guided New York City Department of Health and Mental Hygiene (DOHMH) efforts to reduce exposures by educating the public about risks and benefits of fish consumption-a predominant source of exposure in the general population-and removing mercury-containing skin-lightening creams and other consumer products from the marketplace, from 2004 on (McKelvey et al., 2018). The authors describe changes in exposures over the past decade in relation to these local public health actions and in the context of national changes by comparing mercury concentrations measured in blood (1201 specimens) and urine (1408 specimens) from the NYC Health and Nutrition Examination Survey (NYC HANES) 2013–2014 with measurements from NYC HANES 2004 and National Health and Nutrition Examination Surveys (NHANES) 2003–2004 and 2013–2014. We found that NYC adult blood and urine geometric mean mercury concentrations decreased 46% and 45%, respectively. Adult New Yorkers with blood mercury concentration ≥ 5 μg/L (the New York State reportable level) declined from 24.8% (95% CL = 22.2%, 27.7%) to 12.0% (95% CL = 10.1%, 14.3%). The decline in blood mercury in NYC was greater than the national decline, while the decline in urine mercury was similar (McKelvey et al., 2018). Asian New Yorkers had higher blood mercury concentrations than other racial/ethnic groups. Foreign-born adults of East or Southeast Asian origin had the highest prevalence of reportable levels (29.7%; 95% CL = 21.0%, 40.1%) across socio-demographic groups, and Asians generally were the most frequent fish consumers, eating on average 11 fish meals in the past month compared with 7 among other groups ($p < 0.001$). Asian New Yorkers had higher blood mercury concentrations than other racial/ethnic groups. Foreign-born adults of East or Southeast Asian origin had the highest prevalence of reportable levels (29.7%; 95% CL = 21.0%, 40.1%) across sociodemographic groups, and Asians generally were the most frequent fish consumers, eating on average 11 fish meals in the past month compared with 7 among other groups ($p < 0.001$). Having "silver-colored fillings" on five or more teeth was associated with the highest 95th percentile for urine mercury (4.06 μg/L; 95% CL = 3.1, 5.9).

7.6. Biomarker of effect

At present, there are no validated or widely used biomarkers of mercury effects. Ongoing studies show however, that artisanal gold miners have increased biomarkers of oxidative stress, 8-OHdG (Narvaez et al., 2017). Differences in LINE1 and Alu(Yb8) DNA methylation between gold miners and control group are present in peripheral blood leukocytes. LINE1 methylation is positively correlated with 8-OHdG levels, while XRCC1 and LINE1 methylation are positively correlated with mercury levels. The Long Island Study of Seafood Consumption showed enhanced gene expression patterns of three genes associated with mercury (Monastero et al., 2018). The mean total mercury blood concentration in this cohort was 16.1 μg/L, which was nearly three times the Environmental Protection Agency (EPA) reference dose (5.8 μg/L). The levels of the other metals were consistent with those in the general population. Numerous studies showed that mercury induces cancer in humans and also in animals, in vitro experiments with cultured cells indicate that it causes DNA damage via different molecular mechanisms including release of reactive oxygen species and interactions with DNA repair processes (Nersesyan et al., 2016). In most human studies, positive results were obtained in micronucleus (MN) tests with lymphocytes and excellent agreement with results that were obtained with other endpoints (e.g. chromosomal aberrations and comet formations) (Nersesyan et al., 2016).

In animal models, Gunderson and colleagues observed that methyl mercury decreased (dose dependently) the enzymes glutathione-*s*-transferase (hepato-pancreas), acetylcholine esterase and metallothionein (Gunderson et al., 2018), thus lowering the ability to detoxify environmental contaminants carry out normal cellular processes.

8. Cost burden to the society by human exposure to mercury

As mentioned above, mercury is the subject of a recent global environmental treaty, named the Minamata Convention on Mercury (UNEP, 2013). On 16 August 2017 this global treaty to protect human health and the environment from the adverse effects of mercury entered into force (see Supplementary tool box 2: Minamata Convention on Mercury).

Increasingly, controlling mercury pollution has become a policy goal on both global and national scales. At the same time the demand for assessing the economic gains from avoiding mercury-related adverse health endpoints has risen. The calculation of the cost burden for society by human exposure to environmental pollutants is however not obvious. The causal relationship between polluting agent and disease burden has to be duly supported by the available data, in a context of e.g. multiple or combined exposures. Often authors note that their figures are likely to underestimate the full health effects of pollution. In addition the effects of pollution generally disproportionately affect the poor and marginalized at every level of income, as stated by The Lancet Commission on Pollution and Health (Landrigan et al., 2017). Within the EU GMOS (Global Mercury Observation System) project, Pacyna and colleagues have carried out an assessment of current and future emissions, air concentrations, and atmospheric deposition of mercury worldwide (Pacyna et al., 2016). The combustion of fossil fuels (mainly coal) for energy and heat production in power plants and in industrial and residential boilers, as well as artisanal and small-scale gold mining, is one of the major anthropogenic sources of mercury emissions to the atmosphere at present. These sources account for about 37 and 25% of the total anthropogenic mercury emissions globally, estimated to be about 2000 tons. Projections of future changes in mercury deposition on a global scale simulated by three different models for anthropogenic emissions scenarios of 2035 indicate a possible decrease in up to 50% deposition in the Northern Hemisphere and up to 35% in Southern Hemisphere for the best-case scenario with Maximum Feasible Reduction, as compared to the Current Policies (Pacyna et al., 2016) (see Supplementary tool box 3 for more details on "Current global anthropogenic emissions and on possible future mercury emissions", by Pacyna and colleagues, with Supplementary Figs. 1, 2).

With respect to this mercury emissions, the size of the affected populations, are substantial. Several studies attempted to make an assessment of the costs burden of prenatal exposure to methyl mercury, and the related loss of IQ, and consequently a lower earning potential and a lower production. For example, research from Trasande in 2005 (Trasande et al., 2005) indicated that in the US approximately 300,000 to 600,000 children each year have cord blood mercury levels >5.8 μg/L, putting them at risk of neurological and developmental problems. The resulting loss of intelligence causes diminished economic productivity that persists over the entire lifetime of these children. This lost productivity was calculated to amount to $ 8.7 billion (range, $2.2–43.8 billion). A calculation from 2012 (Grandjean et al., 2012) suggested that current methyl mercury exposures in the US were associated with a total IQ loss for the U.S. population of children 0–5 years of age (n = 25.5 million) to be 1,590,000 IQ points, or 264,000 IQ points per year. Estimating the value of one IQ point at about $18,000, the annual economic loss due to mercury brain drain was estimated at about $5 billion.

An estimated 400 million women of reproductive age in the world rely on seafood for at least 20% of their intake of animal protein; a large share of them live in low- and middle-income countries where access to information on methyl mercury content in seafood is not widely available. Sheehan et al. found that biomarkers of methyl mercury intake were of greatest health concern among three categories of seafood-consuming women and their infants: a) rural riverside dwellers living near tropical small-scale gold mining with diets dependent on locally-caught freshwater fish; b) those in Arctic regions for

whom apex food-chain marine mammals are a dietary staple; and c) coastal inhabitants, particularly in the Pacific and Mediterranean, who probably consume seafood that is primarily commercially sourced. Based on biomonitoring data, the authors applied a dose–response relationship (0.18 infant IQ point lost for every ppm increase in maternal total hair mercury) to estimate the economic costs associated with mercury contamination. The resulting interquartile range of estimated IQ loss spanned from 1 to 13 points for the gold mining, Arctic and coastal subpopulation categories (Sheehan et al., 2014).

In the frame of the discussions on EPA's Mercury and Air Toxics Standards (MATS), a paper published in 2016 in the Proceedings of the National Academy of Sciences (Giang and Selin, 2016), suggested that including a larger set of health effects – namely, both IQ and heart attacks – and the impact on specific populations could lead to mercury-related benefits estimates that are orders of magnitude larger than those reported by the EPA.

In Europe, a recent study (Bellanger et al., 2013) focused on the assessment of the economic benefits of prevented developmental neurotoxicity using distributions of hair mercury concentrations among women of reproductive age from the DEMOCOPHES project (1875 subjects in 17 countries) and literature data (6820 subjects from 8 countries). They estimated that between 1.5 and 2 million children in the EU are born each year with methyl mercury exposures above the safe limit of 0.58 μg/g and 200,000 above the World Health Organization (WHO) recommended maximum of 2.5 μg/g. When analyzed per country, children born in Portugal and Spain were the most exposed to methyl mercury and Hungary the least. When converting the effects of methyl mercury on developing brains into IQ points, the total annual benefits of exposure prevention within the EU were calculated at >600,000 IQ points per year, corresponding to a total economic benefit between 8000 million and 9000 million Euro per year. To our knowledge no economic valuation studies approximating the health costs from mercury use in gold mining have been uncovered specific to the ASGM context. However, with an estimated 4.5 million women working in artisanal mining, many of childbearing age, and 1–2 million children possibly involved in artisanal and small-scale gold mining, with children as young as three years-old working within or outside the family unit, implications for future economic prosperity in those communities will be extensive. Miners in Indonesia, the Philippines, Colombia, Guyana, Zimbabwe, Tanzania and Brazil are found to have mercury levels up to 50 times above World Health Organization limits (UNEP, 2011).

Eagles-Smith et al. (2018) have evaluated global extrinsic socioeconomic drivers associated with mercury exposure in humans (including exposure patterns in different cultures and populations). The authors conclude that in industrialized nations, lower income urban anglers, especially minority and immigrant populations, can be at particularly high risk of mercury exposure because they are more likely to consume self-caught rather than store-bought fish, and often these anglers target predatory species with the highest mercury concentrations. As industrial development continues and economies of different countries shift in response to globalization, population growth, and resource availability, the relative mercury exposure risk in distinctive populations is likely to change in response. Similarly, continued exploitation of fisheries and "fishing down" marine food webs is expected to influence methyl mercury concentrations in common market fish, thereby changing the exposure risk of the regions in which those species are commonly sold. Socioeconomic trends can also influence human exposure to inorganic mercury, particularly from sources associated with ASGM (Eagles-Smith et al., 2018). It has been argued that ASGM is a poverty-driven activity with pertinent micro- and macroeconomic drivers as well as push–pull factors. Biomonitoring surveys of ASGM workers and community members show that they have among the highest mercury exposures of any group worldwide. The mercury exposure risks are further exacerbated by the fact that most ASGM operations are informal (and illegal in many countries) and thus sit outside regulatory and public health support programs (Eagles-Smith et al., 2018).

The WHO suggest that both immediate and long-term policy actions are necessary to reduce the release of mercury and its compounds into the environment in order to protect the children from current and future exposure threats (WHO, 2010). The most important action that national, regional, and international agencies can take is the development and promotion of mercury-free alternatives in the industrial, medical, and occupational sector (WHO, 2010). Technical solutions already exist that could dramatically lower the use and release of mercury in ASGM. These technologies include better pre-concentration of gold prior to amalgamation, decreasing the amount of mercury needed; capture, re-activation, and re-use of mercury; and mercury-free gravity separation technologies. Some researchers have estimated that if all of these techniques were applied together, they would reduce global use of mercury in ASGM as much as 90%.

The WHO has implemented a pilot study (derived from the Minamata Convention) measuring mercury in environment and in human samples in different countries presenting different mercury problems from the point of view of the main exposure route for the population (UN-Environment, 2018a). The objectives of the study are: a) to harmonize approaches for monitoring mercury in humans and the environment and b) to strengthen the capacity for mercury analysis in humans and the environment to accurately determine their concentrations globally.

While much is already known and documented on effects of mercury poisoning, the economic 'translation' of this information is still largely lacking. Such data, however allow these effects to be better integrated into political and financial decision-making (UNEP, 2011).

9. Conclusions

- Mercury pollution poses global human health and environmental risks. Still knowledge gaps exist on both exposures and health effects and translation into preventive actions is delayed.
- Across the globe, differences in mercury contamination and related health effects exist. Understanding the risks associated with mercury exposure is complicated by this element's varied environmental fate and the overarching influences of environmental, biological, and socioeconomic drivers. Increasing land use and climate change, inherently linked to changes in ecosystem function and global atmospheric and ocean circulations, may impact mercury cycling in the future.
- Successful management of global and local mercury pollution and its health impact will require integration of mercury research and policy in a changing world. Research should be swiftly translated in adequate preventive measures and human biomonitoring programs.
- The lesions learned from Minamata show that, there is a need for accurate information about contaminant exposures enabling policymakers to make informed choices (i.e. that balance the benefits of fish consumption against the adverse effects of low-level methyl mercury exposures).

Increasingly controlling mercury pollution, and thereby protecting human health and the environment from its adverse effects, has become a policy goal on both global and national scales. On 16 August 2017 the Minamata Convention on Mercury, a global environmental treaty, entered into force (UN-Environment, 2018b).

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Competing interest/conflict of interest

The authors declare no competing or conflicts of interest.

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